Intrinsically determined cell death of developing cortical interneurons.

Journal: Nature

Publication Year: 2012

Authors: Derek G Southwell, Mercedes F Paredes, Rui P Galvao, Daniel L Jones, Robert C Froemke, Joy Y Sebe, Clara Alfaro-Cervello, Yunshuo Tang, Jose M Garcia-Verdugo, John L Rubenstein, Scott C Baraban, Arturo Alvarez-Buylla

PubMed link: 23041929

Funding Grants: Inhibitory Nerve Cell Precursors: Dosing, Safety and Efficacy

Public Summary:
The formation of the cerebral cortex inhibitory circuits is complex and understanding it is of great value. By determining how inhibitory circuits form in healthy individuals, we will better understand how disease states manifest and open up new avenues for disease treatment. Cortical inhibitory circuits of the cerebral cortex are thought to arise through periods of cell proliferation and programmed cell death of cortical interneurons. Here we report the characterization of typical cell death of mouse cortical interneurons in vivo, in vitro, and after transplantation. We found that 40% of developing cortical interneurons were eliminated during postnatal life. When grown in vitro or transplanted into the cortex, interneuron precursors died at a cellular age similar to that at which endogenous interneurons died during normal development. Transplantation expanded the cortical interneuron population of the recipient by up to 35%, but the frequency of signaling by these cells did not scale with the number of transplanted interneurons. Our findings indicate that interneuron cell death is determined by the cells inherent nature, either cell-autonomously or through a population-autonomous competition for survival signals derived from other interneurons.

Scientific Abstract:
Cortical inhibitory circuits are formed by gamma-aminobutyric acid (GABA)-secreting interneurons, a cell population that originates far from the cerebral cortex in the embryonic ventral forebrain. Given their distant developmental origins, it is intriguing how the number of cortical interneurons is ultimately determined. One possibility, suggested by the neurotrophic hypothesis, is that cortical interneurons are overproduced, and then after their migration into cortex the excess interneurons are eliminated through a competition for extrinsically derived trophic signals. Here we characterize the developmental cell death of mouse cortical interneurons in vivo, in vitro and after transplantation. We found that 40% of developing cortical interneurons were eliminated through Bax (Bcl-2-associated X)-dependent apoptosis during postnatal life. When cultured in vitro or transplanted into the cortex, interneuron precursors died at a cellular age similar to that at which endogenous interneurons died during normal development. Over transplant sizes that varied 200-fold, a constant fraction of the transplanted population underwent cell death. The death of transplanted neurons was not affected by the cell-autonomous disruption of TrkB (tropomyosin kinase receptor B), the main neurotrophin receptor expressed by neurons of the central nervous system. Transplantation expanded the cortical interneuron population by up to 35%, but the frequency of inhibitory synaptic events did not scale with the number of transplanted interneurons. Taken together, our findings indicate that interneuron cell death is determined intrinsically, either cell-autonomously or through a population-autonomous competition for survival signals derived from other interneurons.